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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/726,470	11/29/2000	Daniella I. Zheleva	CCI-014RCE	1635

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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
02/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/726,470	ZHELEVA ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-25,36,41,42,44-47,55-60,62-64,66-72,74-80,82,83 and 85-88* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-21,23-25,64,66-72,74,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 22,36,41,42,44-47,55-60,62,63,75-80,82,83,87 and 88.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Response to Amendments/Arguments

Applicant's amendments and arguments filed October 31, 2007 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below in original or modified form is herein withdrawn. The search has been extended as set forth below.

With regards to the double patenting rejection (10/441,952)- the claims of '952 have been amended such that they are now drawn to the cyclic peptides. While cyclic peptides may be obvious over the linear form (*see Grasso, cited below*), the cyclic form does not render the linear form obvious under double patenting. It is noted that '952 teaches the instant peptides, however they are excluded from the claims and '952 does not qualify as prior art under any statute. Thus, the rejection is withdrawn.

Allowable Subject Matter

The indicated allowability of SEQ ID NO:35 is withdrawn in view of ADAMS (PTO-1449, 12/31/02, A2), relied upon in the rejection below.

Election/Restrictions

Upon review of the application, art rendering obvious SEQ ID NO:35 was discovered. In addition, the art distinctly identifies instant SEQ ID NOs:34 and 38, and thus they have been included in the elected group. Further, SEQ ID NO:28, an obvious variant of SEQ ID NO:35 has been included, as it includes the obvious variation of amidation of the C-terminal.

The species read upon claims 16, 18-21, 23-25, 64, 66-72, 74, 85 and 86, and these claims have been examined on the merits.

Claims 22,36,41,42,44-47,55-60,62,63,75-80,82,83,87 and 88 are/remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. The requirement is still deemed proper and made FINAL.

Sequence Compliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR §§ 1.821- 1.825) in order to effect a complete response to this office action.

Specifically, Applicant's sequence listing and claims are inconsistent with each other. Claim 16, 20, 21, 22, 36, 85 and 86 recite SEQ ID NO:2, however many of the limitations of SEQ ID NO:2 in the claims are not allowed when one looks to the sequence listing. For example, the sequence listing does not allow for deletion of amino acids in SEQ ID NO:2, nor

does it allow for alternative amino acids (substitutions) for a defined amino acid. Additionally, modifications such as reversal of amino acids (e.g. F and X_5) is not allowed by the sequence rules, as such modified peptides are structurally distinct and thus require a unique SEQ ID NO. Additionally, it is improper to identify a substitutable position by a specific amino acid and then indicate that it can be something else (e.g. claim 85 options (b), (d), (f) and (g)). Applicant is reminded that a single sequence identifier cannot be used to define multiple sequences. Here, it appears to the examiner that claim 16 is consistent with the sequence listing as the 'wherein' clause adds further limitations on what is allowed by SEQ ID NO:2. In contrast, as exemplified above, claim 85 is not supported by the sequence listing, and lacks antecedent basis to the sequence listing, as the modifications are beyond those contemplated or allowed in the description of SEQ ID NO:2 therein.

Additionally, sequences are recited in the Figures without corresponding SEQ ID NOs, e.g. Figure 6.

Specification

The disclosure is objected to because of the following informalities:

The specification relies upon the recitation 'SEQ ID NO:2' for numerous distinct sequences throughout the specification, for the reasons exemplified above.

The use of the trademark(s), e.g., Reacti-Bind™ (page 55), has/have been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant should capitalize each letter of the word or include a proper trademark symbol, such as ™ or ® following the word. Further, language such as "the product X (a descriptive name) commonly known as Y (trademark)" is impermissible, since such language does not bring out the fact that the latter is a trademark. Language such as "the product X (a descriptive name) sold under the trademark Y" is permissible. See MPEP § 608.01 (v).

Appropriate correction is required.

Please note, the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Drawings

The drawings are objected to because the figures recite sequences without corresponding SEQ ID NOs, e.g. Figure 6. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be

necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Please note, this may be rectified by indication of the SEQ ID NO in the Brief Description of the Drawings section of the specification.

Claim Objections

Claim 25 is objected to for not ending in a period. MPEP § 804.01(m) states that, "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck*, 36 USPQ2d 1211 (D.D.C. 1995)."

Claims 16, 20, 21, 85 and 86 are objected to for the following informalities:

Claims 16, 20, 21, 85 and 86 use a semi-colon, rather than a colon, preceding the recitation of the Markush group- "group consisting of;".

Claim 85 recites 'i-naphthylalanine' which should be '1-naphthylalanine'.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 21, 64, 66-72, 74, 85 and 86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20, 21, 85 and 86 recite the peptide $X_1X_2X_3RX_4LX_5F$ as SEQ ID NO:2, however in view of the limitations in the claims, and dependent claims therein, claims 20, 21, 64, 66-72, 74, 85 and 86 lack antecedent basis as the sequence listing does not provide support for the various modifications. SEQ ID NO:2 does not provide support for the various modifications, e.g. reversal of X_5 and F, substitution of L or F, etc. are not within the definition of SEQ ID NO:2.

Claim 20 indicates modifications (a), (b), (c) or (d) which is any combination of (a), (b) and (c), however the Markush group of the modifications is improperly presented, as in the current form, all must be present, as they are not in the alternative (lacking 'or' between the options), and are not set off as a proper Markush group ("selected from the group consisting of..."). Thus, it is unclear how one can have a combination of any of the three modifications when all three are required.

Claims 21, 85 and 86 recites 'or' between (f) and (g), however it is unclear as to how (g) is an alternative to (f), and how one selects the alternative. For example, is (g) the alternative to (f), or did Applicant intend 'and'?

Claim 85 recites "(g) phenylalanine is replaced by...", however it is unclear as to which phenylalanine it refers, and thus lacks clear antecedent basis. The peptide sequence contains phenylalanine (F) as the last amino acid and X_5 recites phenylalanine, and thus it is unclear if Applicant is limiting the Markush selection of phenylalanine or the F residue of SEQ ID NO:2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 18-21, 24, 25, 66-72, 74 and 85 are rejected under 35 U.S.C. 102(b) as being anticipated by ADAMS (PTO-1449, 12/31/02, A2).

Adams teaches peptide sequences in Figure 2 (page 6625) that anticipate the instant claims, including: KACRRLFG (p21(N)), HSKRRLIF (p21(C)) and SAKRRLFG (p107). The sequences are taught as being the putative cyclin-cdk2 binding regions.

It is noted that HSKRRLIF is instant SEQ ID NO:34 and KACRRLFG is instant SEQ ID NO:38 (claim 25).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16, 18-21, 23-25, 64, 66-72, 74, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over ADAMS, *supra*, in view of GRASSO (US Patent 6,777,388 B1), BOZYCZKO-COYNE (US Patent 6,310,040 B1) and/or LAWRENCE (US Patent 5,639,726).

The instant claims and teachings of Adams are presented *supra*. The instant claims are additionally drawn to the peptides HAKRRLIF and HAKRRLIF-amide, as well as to general modification where an amino acid is replaced with its D-isomer or the alanine/serine is replaced with glycine.

Grasso teaches the methodology and reasons why one performs alanine and glycine scanning of peptides stating, "In the development of peptide ligands of high potency, selectivity and stability, consideration must be given to the side chain groups of each amino acid residue in a given sequence. Questions regarding their specific requirements for bioactivity can be addressed by alanine (Ala) or glycine (Gly) scan (see e.g., Hruby, et al., 1995. *Ann. N.Y. Acad. Sci.* 757: 7-22). In this approach, each amino acid residue is replaced one at a time either by Ala or Gly, and the effect of the replacement is examined in a receptor binding or in vivo bioassay. For those analogs that retain activity, it is concluded that the side chain group of the particular substituted residue is not important for biological activity. For those analogs that lose activity, the side chain group is assumed to be critical Moreover, it is important that in vitro data be validated in vivo." (column 35, lines 51-65).

Grasso provides additional teachings regarding D-amino acid substitution and the general methodology by which one makes such a substitution stating, "Systematic replacement of L-

amino acids by their corresponding D-amino acid isoforms has been used to ascertain the stereostructural requirements of specific amino acid residues for peptide- receptor interactions, as well as the contribution of secondary structural motifs, (alpha-helix, beta-sheet, beta-tum) to the bioactivity of peptides (see e.g., Eruby, 1993. *Biopolymers* 33:1073-1082). This approach has also been shown to increase the resistance of peptides to enzymatic hydrolysis, and to enhance one or more properties of biologically active peptides, i.e., receptor binding, functional potency or duration of action (see e.g., Doherty, et al., 1993. *J. Med. Chem.* 36: 2585-2594; Kirby, et al., 1993. *J. Med. Chem.* 36:3802-3808; Morita, et al., 1994. *FEBS Lett.* 353: 84-88; Wang, et al., 1993. *Int. J. Pept. Protein Res.* 42: 392-399; Fauchere and Thiunieau, 1992. *Adv. Drug Res.* 23: 127-159)." (column 36, lines 21-37).

Bozyczyko-Coyne teaches various "conservative amino acid replacements" (table 2, columns 25 and 26). The general teaching provides that a D-amino acid is a conservative substitution for the L-amino acid.

Lawrence teaches that, "As is generally known in the art, biologically protected peptides have certain advantages over unprotected, i.e., unmodified, peptides when administered to human subjects. As disclosed in U.S. Pat. No. 5,028,592, incorporated herein by reference, a peptide which is protected, for example, through acylation of the amino terminus and/or amidation of the carboxyl terminus often exhibits an increase in pharmacological activity. Modification of peptides also provides increased solubility in aqueous media." (column 12, lines 54-62).

Here, with regards to the peptide HAKRRLIF (SEQ ID NO:35) and the amide form (SEQ ID NO:28), the difference between the teachings of Adams and the instant claims is that Adams

has a serine as X_2, where SEQ ID NOs: 35 and 28 have alanine. In view of the teachings of Grasso, one would have relied upon alanine scanning to determine the activity and importance of each side chain in the biological activity. Thus it would have been obvious to have synthesized the HAKRRLIF in order to determine the importance of the serine side chain on activity. One would have been motivated to have made such peptides in order to elucidate the importance of all residues, including the X_2 serine. The method of alanine scanning and peptide synthesis techniques required to form such peptides are well known and widely practiced in the art, and thus one would have had a reasonable expectation for success in making the peptide.

With regards to the D-isomer substitution, Grasso provides that D-amino acid substitution is routine in the art to systematically determine the stereostructural requirements of the amino acids in a peptide for receptor binding, and Bozyczyko-Coyne provide that D-amino acids are conservative substitutions for the L-isomer. Thus, it would have been obvious to systematically replace each amino acid with the D-isomer, a conservative substitution, in order to determine the importance of the stereochemical structure of each residue on receptor binding. One would have been motivated to have made such modifications in order to determine which resides are structurally important for binding. One would additionally have been motivated to have substituted the D- for the L-isomer in order to obtain the benefits of decreased enzymatic hydrolysis and to enhance the biological activity of the peptide, as taught by Grasso. One would have had a reasonable expectation for success in making the peptide, as peptide synthesis and D-isomer scanning are techniques widely practiced in the peptide art.

With regards to the amide form, it would have been obvious to have synthesized the amide form of the peptide to increase aqueous solubility of the peptide and to increase the

stability of the peptide. One would have been motivated to have acetylated the peptide to increase the aqueous solubility of the peptide and to obtain the benefit of increased activity from the amidation. Amidation of peptides is a routine technique widely practiced in the peptide arts, and thus one would have had a reasonable expectation for success in making the peptide.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Andrew D Kosar
Patent Examiner
Art Unit 1654

Notice to Comply	Application No. 09/726,470	Applicant(s) ZHELEVA ET AL.	
	Examiner **Andrew D. Kosar**	Art Unit 1654	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: SEQ ID NO:2 defines more than one sequence and does not allow for the multiple variations in the claims and specification

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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